USER GUIDE:

Use of EDQM terminologies for Dose Forms and Routes of Administration for Individual Case Safety Reports in E2B(R3) message

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1. Introduction

This User Guide should be used in conjunction with the ICH E2B(R3) Implementation Guide (IG) and associated documents for electronic exchange of Individual Case Safety Reports (ICSRs)[1]. Specifically, this document applies only to the terms maintained by the European Directorate for the Quality of Medicines & HealthCare (EDQM) that relate to Pharmaceutical Dose Forms (DF) and Routes of Administration (RoA) in E2B(R3) format messages.

1.1. Purpose of this User Guide

The purpose of this document is to provide supplementary information on DF and RoA specified in the ISO standard 11239:2012[2], as used for the electronic exchange of ICSRs according to the ICH E2B(R3) IG. In addition to the DF and RoA standards, ISO 11239 provides standards for regulated information on units of presentation and packaging. The units of presentation and packaging are out of scope of this User Guide.

1.2. Scope

The scope of this User Guide is for EDQM DF and RoA terms, excluding the domain of "veterinary" terms. The specific E2B(R3) data elements are G.k.4.r.9 (Pharmaceutical Dose Form) for DF, G.k.4.r.10 (Route of Administration) and G.k.4.r.11 (Parent Route of Administration (in case of a parent child / foetus report)) for RoA.

1.3. Background

The IG for the E2B(R3) message specification was developed by the ICH E2B EWG for implementation of the ISO/HL7 27953-2 ICSR message exchange standard. Among other data elements, the ICSR contains information about the DF and RoA. While DF may be included as free text and RoA may be indicated by a code list from the ICH E2B(R2) guideline, ICH E2B(R3) adopted a suite of five ISO/HL7 standards for Identification of Medicinal Products (IDMP) in the IG.

[1] ISO/HL7 27953-2: 2011 Health informatics -- Individual case safety reports (ICSRs) in pharmacovigilance -- Part 2: Human pharmaceutical reporting requirements for ICSR. The ICH E2B(R3) package includes the following documents, available via www.ich.org: Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs); E2B(R3) Data Elements and Message Specification; Appendix I (B) to the Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs): Backwards and Forwards Compatibility Recommendations; Conversions for E2B(R2)-E2B(R3) compatibility; Appendix I (C) ICH ICSR schema files; Appendix I (D) Reference Instances; Appendix I (E) Example Instances; Appendix I (F) ICH OID list and ICH code lists; Appendix I (G) to the Implementation Guide for Electronic Transmission of Individual Case Safety Reports (ICSRs): Technical Information; E2B(R3) Data Element Structure in ICSR messages; Appendix I (H) BFC conversion. Clarifying information for implementation is included in a an E2B(R3) Question and Answer (Q&A) document, which is updated on a periodic basis.

[2] ISO 11239:2012 Health informatics -- Identification of medicinal products -- Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging

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The IDMP standards describe requirements for standardised data elements, formats, and terminologies for the unique and unambiguous identification of medicinal products and their constituent components. These standards enable international interoperability and global exchange of information on medicines, at required levels of granularity, across the regulatory and health care communities. In addition, ISO has produced a technical specification for implementation of the standards for pharmaceutical dose forms, units of presentation, routes of administration and packaging[3].

The DF and RoA terms in the EDQM Standard Terms database comply with the ISO 11239 standard. ICH selected EDQM as the maintenance organization for the DF and RoA terms for human medicinal products to be used in ICSRs.
EDQM DF and RoA terms are included in the EDQM Standard Terms database (see https://standardterms.edqm.eu/).
Note that the EDQM Standard Terms database contains terms and definitions to describe pharmaceutical dose forms, routes and methods of administration, containers, closures, administration devices and units of presentation. It also contains agreed combinations of terms, for example, to describe where two or more items are packaged together, or where a pharmaceutical dose form and a container are described using a single term. In addition, it contains patient-friendly terms, which are generally shorter terms that, where justified and authorized by the competent authority, may be used on certain product labels where space is limited.

In 2016, an updated version of the EDQM Standard Terms database was released, introducing additional features such as units of presentation, mapped terms and APIs (application programme interfaces, or web services). In 2017, a further update was released in the form of the current database, which introduced the tagging system that allows the inclusion of 'non-traditional' Standard Terms that are intended only for specific uses such as adverse-event reporting.

The information about downloading the EDQM data using the API provided by EDQM is provided on the following page: https://standardterms.edqm.eu/api/api_doc
However, in order to be able to access the above page you need to first register with EDQM: https://www.edqm.eu/register/
Then request free access to the standard term online lists:

[3] ISO/TS 20440:2016 Health informatics -- Identification of medicinal products -- Implementation guide for ISO 11239 data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging.

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Following registration a helpdesk request to EDQM asking for access to the EDQM API needs to be submitted.

There are two options for download formats (XML or JSON), the preferred format can be obtained by setting the appropriate parameter as part of the request to the API.

The following example API request will download all the RoAs including the "Pharmacovigilance use" terms, it will also include all languages supported by EDQM:

https://standardterms.edqm.eu/standardterms/api/v1/full_data_by_class/ROA/1/1.xml?tags=1

These additional example API requests can be used to obtaining the four Dosage form lists in XML format. The combination of these files create the full set of Dosage forms:

https://standardterms.edqm.eu/standardterms/api/v1/full_data_by_class/BDF.xml
https://standardterms.edqm.eu/standardterms/api/v1/full_data_by_class/PDF.xml
https://standardterms.edqm.eu/standardterms/api/v1/full_data_by_class/CDF.xml
https://standardterms.edqm.eu/standardterms/api/v1/full_data_by_class/PFT.xml

For the purpose of E2B(R3), extract only the terms marked "Human and Veterinary" in the domain value and also set "Current" and "Pending" for the term status.

The EDQM API help page has more information about different requests that can be made to the system (https://standardterms.edqm.eu/api/api_doc).

For additional information, including details on change requests, consult the EDQM website.

1.4. Regional use

The terms provided by EDQM have been deemed suitable for ICH E2B(R3) needs, but specific requirements may vary regionally. See websites of regional regulators for the implementation timelines for accepting EDQM terms and additional regional considerations, as appropriate.

2. Versions/releases

The content of the EDQM Standard Terms database is updated on a continuous basis, with new or revised terms available to users as soon as they are available (see https://standardterms.edqm.eu/).

At the time of finalising the ICH E2B(R3) Implementation Guide, the maintenance organisation for DF and RoA was not yet known. Therefore, data elements for TermID Version Date/Number for the corresponding DF and RoA terms were included as placeholders. Whereas each individual EDQM term has a version number and a version date, it is not required to transmit this information. When transmitting EDQM terms, use the following format:

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three letter code indicating the Concept Class followed by '-' followed by Concept Code.

See Appendix A for proper format. Note that any new E2B(R3) submission should not use deprecated terms. Terms that have a status of "pending" should be treated as "current" terms and are accepted.

During the transition from the ICH code list 14 for RoA to EDQM terms, refer to the Appendix A: Mapping Between Legacy ICH E2B and EDQM Route of Administration Terminology in this document for additional guidance.

3. Pharmaceutical Dose Forms

3.1. Data elements for EDQM TermID and version

When transmitting ICSR messages in E2B(R3) format, DFs are transmitted in fields G.k.4.r.9.2a (Pharmaceutical Dose Form TermID Version Date/Number) and G.k.4.r.9.2b (G.k.4.r.9.2b Pharmaceutical Dose Form TermID).

3.2. Term selection

Select the term that most closely captures the concept provided by the primary reporter. If an appropriate term is unavailable, then populate G.k.4.r.9.1 (Pharmaceutical Dose Form (free text)) as free text.

3.3. Migrating E2B(R2) Pharmaceutical Dose Form text to EDQM terms

While free text in E2B(R2) field B.4.k.7 (Pharmaceutical form [Dosage form]) may be mapped to E2B(R3) field G.k.4.9.r.1 (Pharmaceutical Dose Form (free text)), it is recommended that a TermID be selected from the EDQM Standard Terms list for E2B(R3) field G.k.4.r.9.2b, even if free text is provided in E2B(R2).

3.4. Details of ICH E2B(R3) Data Elements for DF

G.k.4.r.9.2a Pharmaceutical Dose Form TermID Version Date/Number

User Guidance	This data element provides the version date/number for the Pharmaceutical Dose Form TermID.
Conformance	Optional
Data Type	25 AN
OID	None
Value Allowed	Corresponding Version Number of EDQM DF Concept Code.
Business Rule(s)	
	Whereas each individual EDQM term has a version number and a version date it is not required to transmit this information.

G.k.4.r.9.2b Pharmaceutical Dose Form TermID

User Guidance	The pharmaceutical dose form should be provided as TermID using EDQM Basic Dose Form (BDF), Pharmaceutical Dose Form (PDF), Patient Friendly Term (PFT) or Combined Pharmaceutical Dosage Form (CDF) controlled vocabulary. Use the following

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	format: three letter code indicating the Dosage Form Concept Class followed by '-' followed by Concept Code.' If the appropriate EDQM Pharmaceutical Dose Form TermID is not available, free text in G.k.4.r.9.1 should be used.
Conformance	Optional
Data Type	15 AN
OID	0.4.0.127.0.16.1.1.2.1
Value Allowed	EDQM DF Concept Class-Concept Code
Business Rule(s)	
	Examples: BDF-0069, PDF-11008000, PFT-16040, CDF-50041200

4. Routes of Administration

4.1. Data elements for EDQM TermID and version

The E2B(R3) fields are:

- G.k.4.r.10.2a (Route of Administration TermID Version Date/Number) and G.k.4.r.10.2b (Route of Administration TermID)
- G.k.4.r.11.2a (Parent Route of Administration TermID Version Date/Number) and G.k.4.r.11.2b (Parent Route of Administration TermID)

4.2. Term selection

Select the term that most closely captures the concept provided by the primary reporter. If an appropriate term is unavailable, then populate G.k.4.r.10.1 (Route of Administration (free text)) or G.k.4.r.11.1 (Parent Route of Administration (free text)) as free text.

4.3. Migrating E2B(R2) Routes of Administration text to the EDQM Standard terms

E2B(R2) provided code lists for relevant terms for data elements B.4.k.8 (Route of administration) and B.4.k.9 (Parent route of administration (in case of a parent child/foetus report)). For E2B(R3) formatted messages, data elements (G.k.4.r.10.2b (Route of Administration TermID) and G.k.4.r.11.2b (Parent Route of Administration TermID) should be coded using EDQM Standard Terms.

4.4. Details of ICH E2B(R3) Data Elements for RoA

G.k.4.r.10.2a Route of Administration TermID Version Date/Number

User Guidance	This data element provides the version date/number for the Route of Administration TermID.
Conformance	Optional
Data Type	25 AN
OID	None
Value Allowed	Corresponding Version Number of EDQM RoA Concept Code.
Business Rule(s)	

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	Whereas each individual EDQM term has a version number and a version date it is not required to transmit this information.

G.k.4.r.10.2b Route of Administration TermID

User Guidance	The route of administration should be provided as TermID using EDQM Route of Administration (RoA) controlled vocabulary. Use the following format: three letter code ROA indicating the Concept Class followed by '-' followed by Concept Code. If the appropriate EDQM Route of Administration TermID is not available, free text in G.k.4.r.10.1 should be used. For a parent-child/foetus report, this data element indicates the route of administration for the child/foetus (patient). This is usually an indirect exposure, such as transmammary, but can include more usual routes of administration for other drugs given to the child. The parent's route of administration should be provided in G.k.4.r.11.
Conformance	Optional
Data Type	15 AN
OID	0.4.0.127.0.16.1.1.2.6
Value Allowed	EDQM RoA Concept Class-Concept Code
Business Rule(s)	
	Example: ROA-20001000

G.k.4.r.11.2a Parent Route of Administration TermID Version Date/Number

User Guidance	This data element provides the version date/number for the Route of Administration TermID.
Conformance	Optional
Data Type	25 AN
OID	None
Value Allowed	Corresponding Version Number of EDQM RoA Concept Code.
Business Rule(s)	
	Whereas each individual EDQM term has a version number and a version date it is not required to transmit this information.

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G.k.4.r.11.2b Parent Route of Administration TermID

User Guidance	This data element captures the known route of administration of the drug as taken by the parent for the dosage described in G.k.4.r.1 to G.k.4.r.3. The parent's route of administration should be provided as TermID using EDQM RoA controlled vocabulary. Use the following format: three letter code ROA indicating the Concept Class followed by '-' followed by Concept Code. If the appropriate EDQM Route of Administration TermID is not available, free text in G.k.4.r.11.1 should be used.
Conformance	Optional
Data Type	15 AN
OID	0.4.0.127.0.16.1.1.2.6
Value Allowed	EDQM RoA Concept Class-Concept Code
Business Rule(s)	
	Example: ROA-20001000

Further resources

1. References to EDQM

https://www.edqm.eu/sites/default/files/standard_terms_introduction_and_guidance_for_use.pdf

2. References to relevant ISO IDMP documents

IDMP standard for pharmaceutical dose forms, units of presentation, routes of administration and packaging: ISO 11239:2012 Health informatics -- Identification of medicinal products -- Data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging

IDMP technical specification for implementation: ISO/TS 20440:2016 Health informatics -- Identification of medicinal products -- Implementation guide for ISO 11239 data elements and structures for the unique identification and exchange of regulated information on pharmaceutical dose forms, units of presentation, routes of administration and packaging

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Appendix A: Mapping Between Legacy ICH E2B and EDQM Route of Administration Terminology

Mapping of legacy ICH E2B Routes of Administration terms (code list 14) to EDQM terms

ICH E2B(R2) B.4.k.8 Route of Administration *and* **B.4.k.9 Parent route of administration for parent/child/foetus reports** (terms from Attachment 2)		**ICH E2B(R3) G.k.4.r.10.2b Route of Administration TermID** *and* **G.k.4.r.11.2b Parent Route of Administration TermID** (terms from EDQM Standard Terms list)		**Note**
001	Auricular (otic)	ROA-20001000	Auricular use	
002	Buccal	ROA-20002500	Buccal use	
003	Cutaneous	ROA-20003000	Cutaneous use	
004	Dental	ROA-20004000	Dental use	
005	Endocervical	ROA-20006000	Endocervical use	
006	Endosinusial	ROA-20007000	Endosinusial use	
007	Endotracheal	ROA-20008000	Endotracheopulmonary use	
008	Epidural	ROA-20009000	Epidural use	
009	Extra-amniotic	ROA-20011000	Extraamniotic use	
010	Hemodialysis	ROA-20015000	Haemodialysis	
011	Intra corpus cavernosum	ROA-20027000	Intracavernous use	
012	Intra-amniotic	ROA-20022000	Intraamniotic use	
013	Intra-arterial	ROA-20023000	Intraarterial use	
014	Intra-articular	ROA-20024000	Intraarticular use	

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015	Intra-uterine	ROA-20044000	Intrauterine use	
016	Intracardiac	ROA-20026000	Intracardiac use	
017	Intracavernous	ROA-20027000	Intracavernous use	
018	Intracerebral	ROA-20027010	Intracerebral use	
019	Intracervical	ROA-20028000	Intracervical use	
020	Intracisternal	ROA-20028500	Intracisternal use	
021	Intracorneal	ROA-20084000	Intracorneal use	
022	Intracoronary	ROA-20029000	Intracoronary use	
023	Intradermal	ROA-20030000	Intradermal use	
024	Intradiscal (intraspinal)	ROA-20031000	Intradiscal use	
025	Intrahepatic			This term should not be used for future submissions. For R2->R3 conversion: from a data quality perspective it is recommended to check the reporter verbatim and select most appropriate term available from EDQM. If this is not possible, copy 'intrahepatic' to the R3 free text data element for RoA
026	Intralesional	ROA-20032000	Intralesional use	
027	Intralymphatic	ROA-20033000	Intralymphatic use	
028	Intramedullar (bone marrow)	ROA-20036500	Intraosseous use	

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029	Intrameningeal	ROA-20042000	Intrathecal use	
030	Intramuscular	ROA-20035000	Intramuscular use	
031	Intraocular	ROA-20036000	Intraocular use	
032	Intrapericardial	ROA-20037000	Intrapericardial use	
033	Intraperitoneal	ROA-20038000	Intraperitoneal use	
034	Intrapleural	ROA-20039000	Intrapleural use	
035	Intrasynovial	ROA-20024000	Intraarticular use	
036	Intratumor	ROA-20043000	Intratumoral use	
037	Intrathecal	ROA-20042000	Intrathecal use	
038	Intrathoracic	ROA-20039000	Intrapleural use	
039	Intratracheal	ROA-20008000	Endotracheopulmonary use	
040	Intravenous bolus	ROA-20045000	Intravenous use	
041	Intravenous drip	ROA-20045000	Intravenous use	
042	Intravenous (not otherwise specified)	ROA-20045000	Intravenous use	
043	Intravesical	ROA-20046000	Intravesical use	
044	Iontophoresis	ROA-20047500	Iontophoresis	
045	Nasal	ROA-20049000	Nasal use	
046	Occlusive dressing technique			*Non-Current*
047	Ophthalmic	ROA-20051000	Ocular use	
048	Oral	ROA-20053000	Oral use	
049	Oropharingeal	ROA-20055000	Oropharyngeal use	
050	Other	CHECK REPORTER'S VERBATIM TERM		This term should not be used for future submissions.

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				For R2->R3 conversion: from a data quality perspective it is recommended to check the reporter verbatim and select most appropriate term available from EDQM. If this is not possible, copy 'other' to the R3 free text data element for RoA.
051	Parenteral	CHECK REPORTER'S VERBATIM TERM		This term should not be used for future submissions. For R2->R3 conversion: from a data quality perspective it is recommended to check the reporter verbatim and select most appropriate term available from EDQM. If this is not possible, copy 'parenteral' to the R3 free text data element for RoA.
052	Periarticular	ROA-20057000	Periarticular use	
053	Perineural	ROA-20058000	Perineural use	
054	Rectal	ROA-20061000	Rectal use	
055	Respiratory (inhalation)	ROA-20020000	Inhalation use	
056	Retrobulbar	ROA-20061500	Retrobulbar use	

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057	Subconjunctival	ROA-20065000	Subconjunctival use	
058	Subcutaneous	ROA-20066000	Subcutaneous use	
059	Subdermal	ROA-20066000	Subcutaneous use	
060	Sublingual	ROA-20067000	Sublingual use	
061	Topical	ROA-20085000	Topical	Consider use of more specific terms. This term is for ICSR reporting only.
062	Transdermal	ROA-20070000	Transdermal use	
063	Transmammary	ROA-20082000	Transmammary	This term is not intended to describe an authorised route of administration for use in marketing authorisations. It is intended for use in adverse event reporting for pharmacovigilance purposes.
064	Transplacental	ROA-20083000	Transplacental	This term is not intended to describe an authorised route of administration for use in marketing authorisations. It is intended for use in adverse event reporting for pharmacovigilance purposes.
065	Unknown			This term should not be used for future

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				submissions. For R2->R3 conversion: from a data quality perspective it is recommended to check the reporter verbatim and select most appropriate term available from EDQM. If this is not possible, copy 'unknown' to the R3 free text data element for RoA.
066	Urethral	ROA-20071000	Urethral use	
067	Vaginal	ROA-20072000	Vaginal use	

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